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The dopamine hypothesis of drug addiction and its potential therapeutic value

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Dopamine (DA) transmission is deeply affected by drugs of abuse, and alterations in DA function are involved in the various phases of drug addiction and potentially exploitable therapeutically. In particular, basic studies have documented a reduction in the electrophysiological activity of DA neurons in alcohol, opiate, cannabinoid, and other drug-dependent rats. Further, DA release in the Nucleus accumbens (Nacc) is decreased in virtually all drug-dependent rodents. In parallel, these studies are supported by increments in intracranial self stimulation (ICSS) thresholds during withdrawal from alcohol, nicotine, opiates, and other drugs of abuse, thereby suggesting a hypofunction of the neural substrate of ICSS. Accordingly, morphological evaluations fed into realistic computational analysis of the medium spiny neuron of the Nacc, post-synaptic counterpart of DA terminals, show profound changes in structure and function of the entire mesolimbic system. In line with these findings, human imaging studies have shown a reduction of dopamine receptors accompanied by a lesser release of endogenous DA in the ventral striatum of cocaine, heroin, and alcohol-dependent subjects, thereby offering visual proof of the "*dopamine-impoverished*" addicted human brain. The lasting reduction in physiological activity of the DA system leads to the idea that an increment in its activity, to restore pre-drug levels, may yield significant clinical improvements (reduction of craving, relapse, and drug-seeking/taking). In theory, it may be achieved pharmacologically and/or with novel interventions such as transcranial magnetic stimulation (TMS). Its anatomo-physiological rationale as a possible therapeutic aid in alcoholics and other addicts will be described and proposed as a theoretical framework to be subjected to experimental testing in human addicts.

Keywords: addiction, dopamine, rTMS, dopamine agents, VTA, prefrontal cortex

Drug addiction is a brain disease that produces profound modifications in human behavior (Hyman, 2007; Koob and Volkow, 2010), with important negative consequences at various levels, including personal health, employment, family interactions, and society in general (Chandler et al., 2009). Therapeutic possibilities for this devastating illness are, with some rare exceptions, limited to pharmacologic treatments that are largely unsatisfactory (Koob et al., 2009; Leggio et al., 2010; Swift, 2010). From here the necessity to develop new therapeutic hypothesis/interventions independent from those commonly employed.

Transcranial magnetic stimulation (TMS), through generation of an electromagnetic field capable of crossing painlessly through the skull and influencing the underlying brain matter, appears to be a promising candidate for treating addictive behaviors (Barr et al., 2008; Feil and Zangen, 2010) and other brain diseases (Kobayashi and Pascual-Leone, 2003). In brief, this relatively new method allows modulation of discrete brain areas of the awake and conscious subject under study. The pulsatile electromagnetic field generated around the coil crosses the skull and is capable of directly exciting/inhibiting neurons in the underlying cortices (Padberg and George, 2009). Commonly employed as a research tool, TMS is recently affirming its role as a potential therapeutic means approved by the Food and Drug Administration for brain pathologies such as drug-resistant major depression, bipolar syndrome, and negative symptoms of schizophrenia. In the drug addiction field, the therapeutic potential of TMS has been tested in nicotine-dependent subjects (Lang et al., 2008; Amiaz et al., 2009), cocaine addicts (Boutros et al., 2001, 2005; Sundaresan et al., 2007; Politi et al., 2008), and alcoholics (Conte et al., 2008; Mishra et al., 2010). Although the results are certainly encouraging, the disparity of clinical outcomes evaluated in different studies and diversity of pattern/site/methodology of stimulation precludes direct comparisons and hampers firm conclusions. However, in those studies in which craving was measured (Politi et al., 2008; Amiaz et al., 2009; Mishra et al., 2010) significant reductions have been found, thus encouraging further experimental scrutiny. At present, we are evaluating anti-craving and alcohol-intake efficacy of TMS in alcoholics (Addolorato et al., in preparation), short and long-term cocaine intake in treatment-seeking cocaine addicts (Pedetti et al., in preparation), and money/cocaine choice in a lab study of cocaine addicts non-seeking treatment (Martinez et al., in preparation). Nevertheless, the brain site(s) to be stimulated/inhibited and the stimulation parameters (i.e., frequency of stimulation, number of session etc.,) are matters of intense debate and an appropriate rationale is needed.

DOPAMINE AS A POSSIBLE THERAPEUTIC TARGET

The role of central DA systems in the acute effects of drugs of abuse was recognized long ago (Wise, 1980, 1987; Di Chiara and Imperato, 1988). Even before (Ahlenius et al., 1973), attempts were made to prevent human alcohol-induced euphoria through administration of the DA synthesis inhibitor alpha methyl-para-tyrosine. Although theoretically ineccepibile, this approach (reduction of drug-induced DA increments to prevent abuse) is unlikely to have a practical validity as any compound with DA antagonistic (i.e., neuroleptics) properties is known to be aversive in humans. On the other hand, widely documented experimental evidence suggests that the mesolimbic dopamine system is "hypofunctional" in the addicted brain (Melis et al., 2005). In brief, the hypothesis contends that decreased DA function in addicted subjects results in a decreased interest to non-drug-related stimuli and increased sensitivity to the drug of choice (Melis et al., 2005), leading to propose that restoring DA function might be therapeutically advantageous.

Alcohol-dependent *(in the present context the term "dependent," when referred to a non-human experimental subject, indicates a condition in which the subject has shown unequivocally a proof of dependency, i.e., somatic signs of withdrawal)* rats show a profound reduction of spontaneous firing rate and burst firing of antidromically identified Nucleus accumbens (Nacc)-projecting ventral tegmental area (VTA) DA-containing neurons in rats (Diana et al., 1993) and mice (Bailey et al., 2001) resulting in a concomitant reduction of microdialysate DA in the Nacc (Rossetti et al., 1992; Diana et al., 1993; Barak et al., 2011). Further, the reduced dopaminergic activity outlasts somatic signs of alcohol-withdrawal (Diana et al., 1996, 2003) thereby suggesting a role for DA in the lasting consequences of alcohol dependence while excluding the possibility of a DA role in somatic aspects of withdrawal. Further, original (predependence) DA levels in the Nacc are restored when ethanol is self (Weiss et al., 1996) and/or passively administered (Diana et al., 1993, 1996). These observations are paralleled by intracranial self stimulation (ICSS) studies showing that ethanol-withdrawn rats are capable of maintaining the ICSS behavior provided that the stimulus current intensity is increased (Schulteis et al., 1995). This important observation strongly indicates that the neural substrate responsible for maintaining the ICSS behavior is hyperpolarized, or more refractory, in the alcohol-dependent subject as compared with its control. Since the neural substrate of ICSS involves DA axons (Yeomans, 1989; Yeomans et al., 1993) near the stimulating electrode, the results are complementary to those reported above and well support a deficitary function of DA neurons. In addition, the perseverance of the reduction in DA activity (beyond resolution of somatic signs of withdrawal) has also been documented in morphine-dependent rats (Diana et al., 1999), while a dichotomy between DA function and somatic withdrawal has been observed in cannabinoid–withdrawn rats (Diana et al., 1998). Similarly, conditioned heroin withdrawal decreases reward sensitivity (Kenny et al., 2006) which persists well beyond the initial phase of withdrawal. These findings, observed across different addicting compounds and experimental conditions, suggest that DA hypofunction persists over time, although reverting to "normality" (Diana et al., 1999, 2006), eventually with species-specific time course.

In addition to basic literature, reports in humans are also supportive of a compromised role of DA transmission in alcoholics. While alcohol increases DA release in healthy subjects (Boileau et al., 2003) with some gender differences (Urban et al., 2010), a reduced number of DA receptors has been observed (Volkow et al., 1996; Martinez et al., 2005) in alcoholics that appears to be accompanied by a blunted DA release (Martinez et al., 2005, 2007; Volkow et al., 2007). While the reduced number of DA receptors could be, at first sight, be viewed as suggesting an *increased* DA release, it should be noted that by administering the DA inhibitor alpha methyl-para-tyrosine, Martinez et al. (2009) were able to exclude this possibility. Indeed, while healthy controls do show an increased raclopride binding after acute alpha methyl-para-tyrosine administration, cocaine-dependent subjects do not (or to a significantly lesser extent; Martinez et al., 2009). Similar results were obtained with the dopamine releasing agent methylphenidate (Volkow et al., 2007) and amphetamine (Martinez et al., 2005) in alcoholics. Notably, artificially increasing the brain levels of DAD2 receptors, using a replication-deficient adenoviral vector containing the rat cDNA insert for DAD2 into the Nacc, reduces alcohol intake in spontaneously drinking rats, thereby offering the counterproof that a potentiation of DA transmission may have beneficial effects on alcohol-seeking and alcohol-taking, in experimental models (Thanos et al., 2001, 2004). In line with this conclusion, a spontaneous high number of DA D2 receptors has been shown to have a protective role in non-alcoholic members of alcoholic families (Volkow et al., 2006). These findings further support the notion that the number of DA receptors (and consequently DA transmission) inversely correlates with alcohol drinking.

These observations may suggest that "*boosting*" DA neurons to produce more available DA in the synaptic cleft could alleviate some of the symptoms of addiction and alcoholism, thereby acquiring a therapeutic character. In theory, this could be achieved by two different strategies: (1) DA-potentiating drugs and (2) TMS. Both possibilities are discussed below.

DOPAMINE-POTENTIATING DRUGS

Although medications that increase DA activity could be effective in treating alcohol abuse disorders, conflicting results have been produced (Swift, 2010). For example, it was suggested that the DA agonist bromocriptine reduced drinking in alcoholics (Lawford et al., 1995), but a randomized, double-blind, placebo-controlled study using a long-acting injectable bromocriptine preparation in 366 alcoholic-dependent individuals did not find difference in alcohol relapse between medication and placebo (Naranjo et al., 1997). Another example is the stimulant medication modafinil (DA indirect agonist), found to improve cognition in 40 alcoholics with organic brain syndrome, but effects on drinking could not be measured (Saletu et al., 1990). However, modafinil reduced cocaine use in a placebo-controlled study with 62 cocaine-dependent individuals (Dackis and O'Brien, 2005), while another trial did not find differences between modafinil and placebo tested for methamphetamine users (Shearer et al., 2010). While evidence for the use of DA agonists as a treatment for alcohol and/or substance use disorders is inconclusive (Swift, 2010), there has been a revived interest for these drugs, possibly because adequate

neurobiological rationale (Melis et al., 2005) is now available. For example, aripiprazole (Semba et al., 1995; Burris et al., 2002; Shapiro et al., 2003) a partial DA agonist which in principle should antagonize DA when tone is high, whereas should increase DA transmission when basic tone is low, represents a proposed treatment for alcohol abuse disorders (Kenna et al., 2009). Human laboratory alcohol studies have shown that aripiprazole reduces drinking (Kranzler et al., 2008), especially in the more impulsive alcoholic (Voronin et al., 2008). An fMRI study demonstrated that aripiprazole significantly attenuates neural activity in the ventral striatum in response to alcohol cues (Myrick et al., 2010) thereby suggesting a therapeutic potential for cue-induced relapse. Further, a 12-week, double-blind, placebo-controlled treatment study with 295 alcohol-dependent individuals found that aripiprazole initially decreased heavy drinking days compared to placebo, but this significant effect was not present when the target dose of 30 mg was reached (Anton et al., 2008). This trial also showed greater side-effects and greater study discontinuation in the aripiprazole arm, as compared to placebo (Anton et al., 2008). Interestingly, an open-label study of aripiprazole (Martinotti et al., 2009) and a recent human laboratory study (Kenna et al., 2009) suggests that lower doses of aripiprazole (5–15 mg per day) may be better tolerated and still reduce drinking with effects on relapse comparable to those obtained with the opiate antagonist naltrexone (Martinotti et al., 2009).

In summary, dopamine plays a key role in the addiction process, but significant side-effects have limited the use of medications that work directly on the dopaminergic system. The use of DA partial agonists with lower side effect profiles, and appropriate dosing represent important directions for future research in this area.

TRANSCRANIAL MAGNETIC STIMULATION

Increasing DA tone with appropriate pharmacological tools, is only one of the possible strategies. Endogenous activity of DA-containing neurons can be augmented with non-pharmacological tools such as TMS (Strafella et al., 2001) thereby providing, in principle, an adjunct to the "therapeutic arsenal" against addiction, endowed with lesser systemic side-effects and limited contraindications. However, while the rationale is "neurochemical" for pharmacological agents *(neurotransmitter receptors, brain area etc.,)*, it must be anatomically based for TMS. Being that DA-containing neurons are located deeply in the brainstem (thereby making the neurons inaccessible to direct TMS stimuli) it becomes unavoidable to reach them indirectly through neurons located elsewhere in the brain. The dorsolateral prefrontal cortex (DLPfcx) by projecting monosynaptically to the rat (Carr and Sesack, 2000) and primate (Frankle et al., 2006) VTA may serve this function. These studies show a projection from the PFC to midbrain DA neurons, terminating both within the SN proper as well as in the VTA. They arise from a broad region of the PFC, including the DLPfcx, cingulate, and orbital cortices. Indeed, these pyramidal neurons (**Figure 1**) could be exploited as the primary target of the TMS stimulus and their increased activity to produce, ultimately, an enhancement in DA availability in the synaptic cleft in the Nacc. Schematically, the hypothesized circuit (**Figure 2**) would be the following: TMS → DLPfcx → VTA → DA increase in forebrain projection site (i.e., Nacc). In this context, it is imperative to employ stimulation parameters consonant with the physiological activity of the system under study to restore pre-drug DA levels. For instance, it has been shown that DLPfcx stimulation produces bursts in rat DA neurons (Gariano and Groves, 1988; Murase et al., 1993), highlighting the importance of stimulation

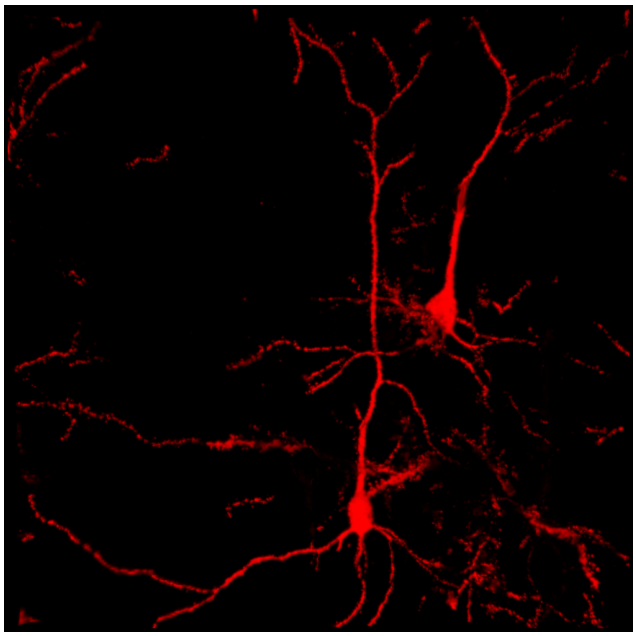

FIGURE 1 | Confocal reconstruction of Golgi-stained pyramidal neurons from DLPfcx obtained by a projection of 55 scans for a depth of 27.5 μm in the *z*-axis. DLPfxc may represent a useful target for rTMS stimulation.

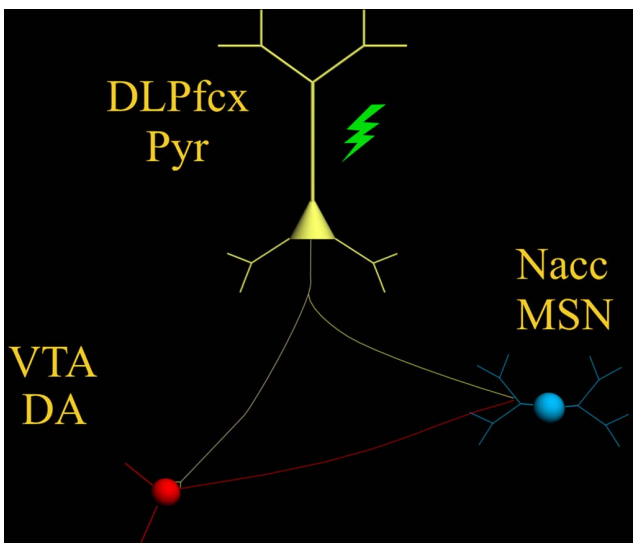

FIGURE 2 | The scheme illustrates the proposed circuit to be activated by the TMS stimulus (green) which, by activating the pyramidal neuron (yellow) with its neurotransmitter glutamate, would excite: (1) DA-containing neurons of the VTA (red) and (2) MSN of the Nacc (blue).

parameters. Indeed, burst firing is more efficacious than single spiking (of identical frequency but evenly spaced action potentials) in inducing DA release in terminal areas (Gonon, 1988; Manley et al., 1992). Consistently, the role of DLPfcx in regulating basal DA activity through the VTA has been reported (Taber et al., 1995; Karreman and Moghaddam, 1996).

Among the various factors that are likely to influence its efficacy, the importance of the baseline cortical activation state on the impact of TMS is fundamental (Silvanto and Pascual-Leone, 2008). This state-dependency is key as the neural impact of any external stimulus represents an interaction with the ongoing brain activity at the time of stimulation. The effects of any external stimulus are therefore not only determined by the properties of that stimulus but also by the activation state of the brain. Accordingly, it has been shown that baseline cortical activity determines whether TMS hampers or hastens behavior (Silvanto et al., 2008). The state-dependency principle described above would also apply to the state of the DA system. The hypodopaminergic state (Melis et al., 2005) should then "amplify" the effect of TMS as compared with that expected in a normo-functioning DA system.

The responsivity of the neuron(s) to electrical and synaptic stimuli is strictly dependent on its morphological features, which in turn, are deeply modified by drugs of abuse (Robinson and Kolb, 2004) and withdrawal from chronic treatment with opiates (Sklair-Tavron et al., 1996; Spiga et al., 2003, 2005), cannabis derivatives/analogs (Spiga et al., 2010), and psychostimulants (Robinson and Kolb, 1997) have been shown to produce reductions in DA cells size (Sklair-Tavron et al., 1996; Spiga et al., 2003), paralleled by persistently (Diana et al., 2006) altered patterns of synaptic connectivity, and spines density in the Nacc and Pfcx (Robinson and Kolb, 1997). These architectural changes would be expected to modify intrinsic spontaneous action potential generating capacity and responsiveness of the system to the TMS stimuli. Accordingly, realistic computational analysis (Spiga et al., 2010) of cannabis-dependent rats, generated by input of experimentally verified morphometrical and electrophysiological properties, predicts a lower action potential generation of Nacc medium spiny neuron (MSN). These results suggest that MSN, of cannabis-dependent rats are likewise hypofunctional. Considering that the main drive of these neurons is cortical glutamate (Glu; see discussion in Spiga et al., 2010, and references therein; Kalivas and Hu, 2006) it raises the possibility of a reduction of Glu as a causal factor. This finding, thus offers the additional possibility that stimulation of these units through TMS may be advantageous in restoring pre-drug physiological activity. Indeed, TMS cortical application should increase the activity of glutamate-containing cortico-fugal fibers monosynaptically impinging upon the spine's heads of Nacc MSN (Groenewegen et al., 1991). Considering the fundamental role Glu plays in synaptic plasticity (Russo et al., 2010), its role could also be exploited in LTP-like stimulation parameters, ultimately aimed at producing lasting and enduring restoration of original physiological activity. These characteristics must be considered and coherently inserted into a framework to obtain optimal stimulation parameters. *In vivo* recordings of VTA-projecting DLPfcx neurons do fire spontaneously around 4–6 Hz (Pistis et al., 2001) and a TMS stimulus frequency of 10 Hz could be a reasonable frequency to obtain a significant increase in VTA-projecting neurons aimed at stimulating the "*deficient*" dopamine system and its post-synaptic counterpart (i.e., MSN of the Nacc).

Another factor to be considered is that all previous studies (see above) applied the TMS stimulus monolaterally, yet obtaining a reduction of alcohol craving (Mishra et al., 2010). While alcohol intake was not measured, and contralateral effects cannot be excluded *a priori*, it is possible that application of TMS bilaterally, as in the case of the H-coil (Feil and Zangen, 2010), would yield stronger cortical activation (larger number of fibers activated) with an increased probability of a significant increment of bilateral DA release. It should be noted that unilateral TMS application has already been reported to increase DA release (Strafella et al., 2001) omolaterally in the human striatum, as well as in rodents (Keck et al., 2002; Zangen and Hyodo, 2002), and even in morphine-withdrawn rats (Erhardt et al., 2004), thereby supporting the rationale outlined above. Although Strafella et al. (2001) proposed activation of (Glu-containing) cortico-fugal fibers making synaptic contact with DA-containing terminals in the ventral striatum, to explain their results, it should be noted that the existence of axo-axonic contacts has always being questioned based on the lack of appropriate anatomical observations (Groenewegen et al., 1991; Meredith et al., 2008).

While many technical details for optimal stimulation parameters need further investigation and optimization, the TMS appears to deserve careful experimental scrutiny as a potential therapeutic tool in alcoholics and other addicts. Indeed, with its nearly absent systemic effects, minimal side-effects, and a low degree of invasiveness, TMS may offer the first opportunity for an efficacious, non-pharmacological, therapeutic tool in alcoholism and other chemical dependencies. If appropriately combined with a solid neurobiological rationale (DA system), it may offer a unique opportunity for developing further the first "*electrophysiological*" approach in studying and eventually treating the devastating and widespread brain disease of addiction.

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